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EDITORIAL

On these pages the editor offers his opinions, unshackled by advertising patrons and unrestrained by anything save a sense of the decent and the truthful. The editor, alone, is responsible for their type, their tone and their tenor.

WILLIAM PROCTER, JR.

WILLIAM PROCTER, JR., lived in those staid and steady Philadelphia days when, in between the cobble stones, the grass grew green on High Street—and the wood thrush still maintained his nest—and sang his merry song on the banks of a clear blue Schuylkill.

It was the golden, quiet Quaker age of Philadelphia town—when even progress moved on silent wheels and the gentle hand of peace was on the land and people.

They were the days, before the whirlwind—those mellow, fallen days when art was strangely short and time not half so fleeting.

Such were the days—and here the place, where William Procter worked, in serious Quaker company—with diligent and forward-looking minds—not merely marking time of day and strengthening their present, but striving, earning rich tomorrows for us, their children yet unborn.

How unlike now, when government by man promptly makes bad debts—instead of better deeds—to count as their inheritances.

But the Quaker way was a different way, and Procter was a Quaker. He was born of such English parents, then residents of Baltimore, on May the 3d, in 1817. In 1831, having lost through death his splendid father, the youth removed to Philadelphia and associated himself with another young lad, Joseph Turnpenny. Together they were apprentices to the Zollickoffer Pharmacy at Sixth and Pine Streets, yet failed to find their work a daily grind in spite of all their grinding. Here his young mind received its first lessons in pharmacy. In 1837 he was graduated from the College, the subject of his thesis being "Lobelia Inflata"; three years later was elected a member of the College, the beginning of a long period of signally notable services to the institution and to pharmacy generally.

He quietly continued his work in Zollickoffer's store, studying diligently and making journeys for recreation and improvement, from time to time, to various parts of the country—to Washington, to Ohio, returning by way of Niagara Falls, to Boston by sea, and to

other places, recording his botanical and other observations as he proceeded. Meanwhile he was reading diligently in his leisure hours.

Already he had made the acquaintance of some of the principal scientific workers of the city. In 1841, though only twenty-four, he was secretary to the Committee of Revision of the Pharmacopœia and supervised their even then extensive pharmaceutic research. He was also active on the committee of the College at work on the same subject, while his activities on the successive revisions of the Pharmacopœia were untiring and of the greatest practical value.

In 1846 the College took a most important step forward when it divided the chair of materia medica and pharmacy (which had been in existence since 1821) into two—one chair on materia medica, and the other on pharmacy; and William Procter, Jr., was unanimously elected the first professor of pharmacy, and the high character of his lectures and their evident practicality brought him instant fame and appreciation.

There was no subject which enlisted his attention so much as the advancement of his College. For a time he was associated with Carson as co-editor of the AMERICAN JOURNAL OF PHARMACY, and upon the latter's retirement Procter assumed sole editorial charge, a position which he held until he was succeeded by John M. Maisch. For twenty years the journal was a reflection of this man's active outreaching mind. He filled its pages with valuable material adapted to the needs and contributing to the education of American pharmacists, while the publication increased the reputation of its editor and the College which sponsored it. His own service as an author and as a constant experimenter in the field of drugs, is made apparent when it is known that there are 550 original articles in the journal to which his name is attached, exclusive of extracts and editorials. In 1849 he issued his American edition of Procter and Redwood's "Practical Pharmacy," a voluminous work enriched by many additions from his pen.

The American Pharmaceutical Association was the offspring of Procter's able and versatile mind. Throughout the years of his life which followed the organization of that body, he gave to it the richest treasures of an intellect fitted beyond all others for the work which he had undertaken. In 1853 he was chairman of the committee on the progress of pharmacy, and chairman of a committee to report a syl-

labus of a course of study for students of pharmacy, which committee reported in 1858. He was corresponding secretary of the Association from 1852 to 1857, first vice-president in 1859-1860, and was elected president at its session held in Philadelphia in 1862. And the pharmacists of America have not allowed the name of their most distinguished colleague to fall into oblivion. They have kept the memory of William Procter, Jr., green in their hearts, and have given a monument of signal grace in a signal place in Washington, but even better than that they have given him a memorial more lasting than stone or bronze, a monument built in their affections and in the affections of those who come after them.

The character and extent of Procter's services to his profession made him truly 'The Father of American Pharmacy," and it is fitting that his Alma Mater now perpetuates his memory with the Procter International Award, awarded periodically to leaders in the field of pharmaceutical research.

Procter resigned the chair of pharmacy in 1866, and it was occupied one year by Maisch, but the latter, in 1867, exchanged chairs with Parrish, then professor of materia medica, who became professor of the theory and practice of pharmacy, and continued in this position until his demise in 1872, when Procter was persuaded to return to the place. This second period of service covered only two years, for he died February 10, 1874. On a Tuesday afternoon in February, 1874, with the winds of winter hurling snow against the window panes on the second floor of the small new school on Tenth Street, Dillwyn Parrish, in somber Quaker garb, addressed the College membership. Said he: "On Tuesday morning, the 10th inst., the intelligence was spread among us that Professor Procter had died during the night. So overwhelming was the sense of the loss we had sustained, that our hearts were mute with grief.

"Slowly, but not with less impressiveness, comes to us the realization that the voice, so lately heard in instruction and in counsel within these walls, is now sealed in death. While mourning a loss which seems to us almost irreparable, it is fitting that we should call to remembrance the many benefits which the life of our brother has bestowed upon us. For a quarter of a century his name has been inscribed on our banner, and we have found it a talisman of strength.

"His life was characterized by earnestness of purpose, single-minded in pursuit of science, sincere in all his relations in life, loving Truth for Truth's sake; his enemies are unknown, but friendship is claimed wherever his name is spoken.

"The record of his life is engraved on the character of this institution; our JOURNAL is an enduring monument of the activity and ability of his genius. His name comes back to us from beyond the Atlantic in pharmaceutical literature with acknowledged authority. Well may the drapery of mourning be hung upon these walls, and our eyes turn in depressing sadness to the vacant chair.

"There can be no tribute paid more fitting to the character of our brother than the many hearts which mourn his loss. It remains for us to remember his example and to strive to emulate his labors, so that his life may be renewed in that spirit and power which he has left to us as an heritage."

Said another: "Professor Procter loved research and was an untiring worker. He had an earnest and inquiring mind and was full of energy. In manner he was unostentatious and retiring. He was an observer rather than a talker, yet possessed the ability of expressing himself in clear and pleasant language. As a lecturer he was didactic. The jewels of his character were integrity, sincerity and a just sense of duty to his fellows. He was happy in the use of his pen, and his essays were marked by clearness of expression and carefulness of detail. His investigations evidenced a faithfulness in research and a completeness which have made his name an enduring authority."

IVOR GRIFFITH.

ORIGINAL ARTICLES

AN IMPORTANT RESPONSIBILITY OF THE PHARMACEUTICAL EDUCATOR*

ONE never relishes being thought of as a person who seldom does what he is supposed to do, or still worse, what he has agreed to do, even though his many offenses are no more serious than failure to talk to assigned topics.

Sometimes, however, we grow in wisdom while writing a thesis on an assigned subject and, as a result, vary our presentation. I recently learned of a graduate student at one of our large neighboring universities who chose as a problem of research for his doctor's degree "World Unemployment, Its Cause and Cure". I am sure we all admire the ambition of this young man, who, after laboring for over two years, presented a thesis which was accepted by his graduate committee. The title of the thesis as finally accepted read, "Unemployment in the Laundry Industry in Bay Ridge, Rhode Island." This young man had very definitely gained in wisdom during the pursuance of his research studies.

The title of my paper, as read by our worthy chairman, is one which was agreed upon by Dean Sturmer and myself with the thought in mind that it would be almost impossible to prove disloyal to so broad and comprehensive a subject.

It is not surprising that I should feel very severely challenged by the responsibility which I have assumed in connection with these most pleasant ceremonies.

Many persons have flown across the Atlantic Ocean since Charles Augustus Lindbergh landed in Paris, France, during the spring of 1927, but none have won the appreciation and recognition afforded to him. *He* was the pioneer. He went *before*. He *prepared* the way and is still doing his full share toward assuring continuous progress in this important field of transportation. The name of Charles Augustus Lindbergh will always occupy a high place in the field of aviation.

Many colleges of pharmacy have been organized since the Philadelphia College of Pharmacy opened its doors to a small group of

*An address given by Dr. Ernest Little, Dean of the New Jersey College of Pharmacy, at Founders' Day Exercises of the Philadelphia College of Pharmacy and Science, February 23, 1939.

students during the fall of 1821. We are pleased to recognize *this* college as the pioneer in a highly important field of professional education. Its founders went before. They blazed the way, and the college which they organized is still making substantial contributions to the training and education of pharmacists. These early pioneers imposed heavy responsibilities on all who may follow in their footsteps, and even on those who play such relatively insignificant parts as speakers at its Founders' Day exercises.

It is a glorious heritage which the administrators of this college and their staff members have received from those who have gone before. We are certain that they will continue to exert every effort and influence to insure that the torch of this grand old college is kept aloft and that it burns ever brighter with the passing of the years. We are certain also that they will prove successful in their endeavor.

Founded immediately following the appearance of the first United States Pharmacopœia, the Philadelphia College of Pharmacy and Science has made steady continued progress, and is today classed among the leaders in this professional field.

The important pharmaceutical developments which have had their origin in the City of Philadelphia, and in this College, are too numerous to even enumerate on an occasion such as this.

One of these more important early events was the founding of the JOURNAL of the Philadelphia College of Pharmacy in 1825, the name of which was changed to the AMERICAN JOURNAL OF PHARMACY about a decade later. Many early milestones in the life of our profession, as well as profound later developments, are recorded in the pages of this earliest of pharmaceutical journals in this country.

It was here that the first United States Dispensatory made its appearance in 1833, the product of years of hard, faithful preparation on the part of its co-authors, Wood and Bache.

Although the first United States Pharmacopœia appeared shortly before the Philadelphia College of Pharmacy was founded, we are all familiar with the vital role which this college has played in pharmacopœial work and with the continued contributions which it has made to each succeeding revision as they have appeared at ten-year intervals. This steady improvement in the quality and usefulness of the United States Pharmacopœia has unquestionably risen to an all-time high in the United States Pharmacopœia XI, a volume of which Chairman Cook may very properly be proud.

The strengthening and continued development of the American Pharmaceutical Association has grown to be somewhat of a mania with your speaker during the past several years. It seems quite clear that if pharmacy is to achieve its maximum accomplishment it must have a strong parent organization in which anyone connected with any phase of the general field of pharmacy and interested in its welfare is eligible for membership. Its limited membership indicates either a woeful lack of appreciation of the things which are vital to the welfare of our profession or an inexcusable laxity on the part of many people in playing their part in its development.

You will never know the restraint which I have had to exercise in order to refrain from using the remainder of my allotted time in presenting a brief for the American Pharmaceutical Association and enlarging upon the possibilities of its usefulness if properly appreciated and supported.

It is interesting to note that this oldest of national pharmaceutical associations had its inception in this city, under the guidance of officers and staff members of this college. Among the questions discussed at the first convention of this association held in October, 1852, we find "The Sale of Poisons," "The Secret Medicine Business," and "Pharmaceutical Education." I venture the opinion that in one form or another these questions have been before each succeeding convention during all the intervening years.

It is but recently, perhaps during the past ten years, that the development in pharmaceutical education has reached the point where many of us feel that our objectives for many years to come should be the continued strengthening of our program as it is now set up.

Within a few years we have developed from a part-time two-year program to a regular orthodox four-year Bachelor of Science curriculum which has won recognition and respect in high university circles.

The next step seems to many of us to be the development of a graduate program rather than a fifth or sixth year of college work preliminary to the Bachelor's degree, as is already being agitated by some few ultra enthusiasts.

Although our progress during the past twenty years has been rapid and profound there has been little or no question as to the wisdom of the program. There was agreement among leaders. The next step was always very definitely clear. We were following a well-

trodden path with little chance of serious mistake. Such is no longer the case. The path ahead has narrowed almost to the point of extinction. Even the tracks of pioneers are but vaguely discernible. Caution must be exercised or damaging mistakes may follow.

I am preaching no doctrine of contentment with past progress. Such an attitude leads to stagnation and retrogression. I quite agree that the surest thing about progress is that it must be continued. My only caution is that we should if possible be as sure in the future that our newly adopted policies constitute progress as we have been in the past. Lasting progress more frequently results when enthusiasm is accompanied by wisdom and when we feel no great urge to sacrifice security for mere speed. We cannot always see the end of the road at all clearly, but one thing we can and should do, and that is to see that we are at least headed in the right direction.

It does, therefore, seem especially fortunate that the American Council on Pharmaceutical Education should have been organized at just this time. Is it not reassuring that helpful agencies of this sort have a way of appearing at a time when they are most needed?

For many years we have realized the need of more adequate if not more accurate means of accreditment for colleges of pharmacy in this country. The American Association of Colleges of Pharmacy has done an acceptable job, but I doubt if it was ever intended to become an accrediting agency.

The Boards of Pharmacy have performed such a function, so far as was made necessary by the responsibilities resting upon them in their respective States. There is, however, considerable variation, perhaps even variance, in and between the standards of various boards, and adequate co-ordination is lacking.

May I, in passing, pay a sincere tribute to the Boards of Pharmacy in this country. It has become increasingly clear to all of us that we never could have made the progress which has been made in the field of pharmaceutical education, were it not for the intelligent understanding of our problems on the part of our Boards of Pharmacy and the efficient help which they have given us. They have been effective helpmates in every one of our more worthy achievements. Especially may I acknowledge and compliment their admirable leader, who has come to be known as the "Rock of Gibraltar of American Pharmacy," Mr. H. C. Christensen.

The present set-up of the American Council on Pharmaceutical Education is a happy one. We have confidence in the organizations participating. Especially do we appreciate the interest and co-operation of the American Council on Education. We have equal confidence in the individuals whom these various organizations have chosen to represent them. We pledge them our support and active co-operation in every possible way.

I look forward to the time when the American Council on Pharmaceutical Education may become an endowed institution which can make its influence felt to a far greater extent than as merely an accrediting agency. I vision the work of special committees, appointed by the Council and answerable to it, studying such problems as adequate curricula, educational costs, entrance requirements, minimum qualifications for teachers, and other fundamental questions which are of special importance to our profession.

I wonder if the membership of the Council might be wisely increased and broadened. Would it be advisable to add a physician, a dentist, or even a layman as members? I am not prepared to answer these questions. I would like to see them given serious consideration by the Council members. They are in a position to render the wisest decision and to take such action as seems appropriate.

It seems rather certain that our present program of pharmaceutical education as it has developed to date is not unsound and that its future will be adequately safeguarded.

In the field of retail pharmacy we hear all sorts of dire comments and predictions. Pharmacy is decadent. It advertises itself as a profession and conducts itself in a manner which leaves much to be desired, etc., etc. You have heard them all. I shall make no attempt to answer such extravagant statements, but will simply express a personal opinion for what, if anything, it may be worth.

Keeping in mind the training and education of the modern pharmacist and evaluating as best I can future public health needs, it seems quite definite that the professional services of the retail pharmacist will be needed and utilized on an increasing scale in the years ahead.

In regard to the merchandising activities of retail pharmacists, I shall make scant comment. Frankly, I am not as profoundly shocked by the fact that the retail pharmacists' responsibilities are a combination of business and professional activities as some educators profess to be. I feel that pharmacy, and every other line of endeavor, should

be allowed to evolve in such a manner as to best fit into the general scheme of things. Should we attempt to force retail pharmacy to develop in such a way as to bring it to the greatest measure of respect and acclaim as a profession, if its greatest usefulness and most effective service to the general public can best be accomplished by a somewhat different development?

I am just a little hesitant about making the following statement, but I believe that my attitude and spirit will not be misunderstood. I am not so much interested in dignifying pharmacy as I am in enabling it to contribute its greatest possible service to the general welfare, keeping in mind at all times that its primary field of activity is that of public health.

On the other hand, I have little patience with the type of merchandising activities of some retail pharmacists. It is also discouraging to find retail pharmacists looking to such legislation as the Robinson Patman Bill, Fair Trade Laws, and the fair trade decision of the United States Supreme Court as the most important means of promoting their future security. It is discouraging to see evidence that the retail pharmacist sometimes fails to realize that his most profound and enduring security will be realized when he can stand forth as a professional man whose legislative needs are few, due to the fact that he is prepared to render an important professional service which few individuals are prepared to render. Only thus can he realize and enjoy the sort of security which comes, not as a gift, but as the result of hard work and the attainment of a certain degree of perfection in a professional or otherwise important field of endeavor.

There is no reason for undue pessimism as to the future of retail pharmacy. There is definite evidence that the apparent conflict between business and professional activities is gradually resolving itself in a satisfactory manner, not because of any legislative measures but because of natural evolutionary changes. The concentration of prescription work in some stores and of merchandising activities in others seems very definitely to indicate the eventual separation of the drug store and the pharmacy as is now the case in many European countries; each offering to their community a highly important service, one of a commercial and the other of a strictly professional nature.

It does not seem contradictory for me to close this part of my address with the thought that the chief responsibility of our colleges

of pharmacy is that of providing our students with adequate professional training without giving undue consideration to the standards of the market place, except as we may lend our influence to keep them on as high a plane as possible. We should exert every influence in the direction of making it unlikely that the business activities of the retail pharmacist will eclipse his professional responsibilities or weaken his desire and determination to function to the fullest possible extent as a reliable professional man.

In conclusion, I would like to comment briefly on what I consider to be our greatest of all responsibilities, that of awakening in our students not only an appreciation of proper moral standards but the acceptance of a philosophy of life which will serve as a never-failing guide through troublesome uncertain times and which is closely akin to religion.

If we are to look to the future with any feeling of security, it is essential that the men and women who are leaving our college halls should realize and appreciate that this world, this universe in which we live, is a rational universe; that things do not happen in a haphazard hit-and-miss sort of way but in accord with law and order such as we see demonstrated every day in the field of science.

I suppose the above statement amounts to the same thing as saying that they happen in accordance with a plan, which plan may at times be tremendously involved—in fact, so much so that we are unable to fully understand or comprehend it—but which is wonderfully complete and for which a supreme intelligence which we choose to call God is responsible.

On such a foundation we can build with confidence and courage. Without it we have no guarantee of permanence or any special virtue upon which to base any such expectation.

May we accept this challenge as the greatest of all responsibilities of the modern educator and may we be given the strength and wisdom and courage to achieve results which are acceptable in his sight.

It has been a privilege to be permitted to meet with you this afternoon. I thank you for your courteous attention. I hope that today's exercises may some day be thought of as an event in the early infancy of this college and that the Philadelphia College of Pharmacy and Science will during all these years render an increasing service to pharmacy and the other branches of science which it is today serving so well.

HYDROGEN ION CONCENTRATION AND CYANOGENESIS IN SORGHUM

By James F. Couch and Reinhold R. Briese

Contribution from the Pathological Division, Bureau of Animal Industry, Washington, D. C.

IT HAS been known for a long time that mixtures of cyanogenetic plants and water that have been acidified or alkalized develop much less hydrocyanic acid than do mixtures that have not been so treated. Very little of an exact nature is known about the mechanism of this phenomenon. Our knowledge of it is based on investigations carried out several decades ago when the concept of hydrogen ion concentration had not reached its present importance. The acid and alkali solutions added to the cyanogenetic mixtures were defined in terms of normality and no indications of the pH of the resulting mixtures are available. It seemed necessary, therefore, to reinvestigate the subject from this standpoint; to determine whether the phenomenon is determined only by the pH of the mixtures or whether the nature of the added acid is a factor. It was also of interest to determine whether any difference in effect could be distinguished between organic and inorganic acids.

Historical Summary

Auld (7) reported that acids and bases inhibit the action of emulsin on amygdalin; that this enzyme prefers a neutral medium and that its action is restored to a great extent by neutralization of the inhibiting acid or alkaline media. He found (8) that pepsin in 0.2 per cent. HCl inhibited the formation of HCN in linseed cake. He states (9) that under digestive conditions cyanogenesis in linseed cake is likely to be inhibited by acids and alkalies and that, in the rumen, inhibition is caused by the alkaline character of the salivary juices. Collins (17) showed that hydrochloric, butyric, and lactic acids retarded the rate of evolution of HCN from linseed. He concludes "Under the conditions of animal digestion, the acidity is of the highest importance. With normal health, the acidity of the stomach is too high to allow linseed to evolve hydrocyanic acid, but there may be abnormal circumstances when the production of hydrocyanic acid

would set in." Collins and Blair (18) reported that HCl inhibits the enzyme in linseed and stated that linseed cannot produce HCN in non-ruminants because the stomach acid prevents the enzyme from acting. Gerloff and Ostermann (25) found that linseed powder that produced 25.4 mg. per cent. of HCN gave with 0.05N HCl, 25.4 mg. per cent. and with 0.0333N HCl, 25.2 mg. per cent. and concluded that the acidity of the human stomach is insufficient to hinder the production of HCN from linamarin. Guignard (26) observed that the gastric juice of a pig did not hydrolyze linamarin (from *Phaseolus lunatus*) but that HCN was formed when the enzyme from the same plant was added to the mixture. Swanson (36) in an extensive study of cyanogenesis in Sudan grass found that N, 0.1N, and 0.2N sulfuric acid completely inhibited cyanogenesis in a sample that gave 15 mg. per cent. with water; 0.01N and 0.02N acid gave 5.5 and 2 mg. per cent., respectively, from a Sudan grass sample that gave 5 mg. per cent. with water. Hydrochloric and phosphoric acids gave similar results. Solutions of NaOH and Na_2CO_3 stronger than 0.02N also markedly diminished the yield of HCN. Addition of the acids or of NaOH to Sudan grass macerated in water cut down the yield of HCN by 40 to 60 per cent. Swanson fed ten pounds of green sorgo to a horse without effect and implies that the acidity of the horse's stomach prevented poisoning.

Riet and Echenique (31) studying the Guiguard test as applied to Sudan grass found that the addition of 2 cc. of 2 per cent. acid to 5 g. of plant acetic, tartaric, sulfuric, and hydrochloric acids, enhanced the color produced but that larger quantities gave a reduced or negative test. After neutralizing the plant the addition of 2 cc. of 0.1N NaOH gave a negative test. With water alone the pH of the plant mixture ranged from 4.5 to 6; after adding the acids the pH was 3.1 to 4.5. Addition of 1 cc. of 2 per cent. acetic acid gave a pH of 3.8 to 4. They conclude that the Guignard reaction does not require a special pH but that extremes of acid and alkali must be avoided. Askew (6) found that the HCN yield from white clover was reduced by 0.001N and 0.01N sulfuric acid. 0.001N and 0.01N NaOH had little effect but 0.1N NaOH cut the yield 75 per cent. Bertrand and Compton (12) found that adding a small quantity of sulfuric acid to the reaction mixture accelerated the hydrolysis of salicin by emulsin.

Willaman (41) found that 5 per cent. solutions of sulfuric, nitric, and tartaric acids had little or no hydrolyzing action on amygdalin and that 2 per cent. HCl hydrolyzed 26.5 per cent. after seventy-two hours' boiling. This was contrasted with a 98.5 per cent. hydrolysis effected by emulsin in twenty-four hours at 45 degrees. Willaman states that grinding sorghum leaves with 5 per cent tartaric acid prevents enzyme action.

Briese and Couch (14) observed the effects of acids in varying strength on sorghums, wild cherry, Sudan grass and arrowgrass and found a diminution in the yield of HCN except in one instance with dilute tartaric acid. The effects of the acids were in general proportional to the concentration and ionization constant of the acids used.

Jacobson (27) observed that KOH accelerated the peroxidase activity of emulsin from almonds until the free acidity of the H_2O_2 was neutralized and then retarded the activity. HCl and HCN markedly retarded this activity. He showed that the peroxidase action of emulsin was distinct from its action on amygdalin since the enzyme preparation was highly active towards the glucoside after it had ceased to evolve oxygen from the peroxide.

Since in all of the cases studied cyanogenesis is the result of the hydrolysis of a nitrile glucoside by an enzyme it is to be expected that the reaction will proceed most rapidly at some particular pH value. Vulquin (37), using buffer mixtures, HCl, H_2SO_4, and Na_2CO_3, with amygdalin and emulsin, found that after an hour's reaction he obtained maximum yields of HCN at hydrogen ion concentrations between 0.2×10^{-5} and 0.6×10^{-5} (or pH 5.69 to 5.22). Willstätter and Csányi (44) report the optimum pH for the glucosidase action of emulsin on amygdalin is 6, and on prunasin, 4.9. Willstätter and Oppenheimer (45) found the optimum pH for the hydrolysis of salicin, helicin, arbutin, and B-phenyl-glucoside by emulsin is 4.4, 5.3, 4.1, and around 5, respectively. Kuhn (30) found pH 5.5 favorable for the hydrolysis of maltose by emulsin. Antoniani (2) reported the optimum pH for the β-glucosidase from *Sorghum saccharatum* seed as measured by the hydrolysis of cellobiose and salicin to be 4.6. Bertrand and Compton (11) found that amygdalin and amygdalase reach optimum activity in a medium neutral to phenolphthalein.

With the exception of the determinations by Vulquin the pH figures reported by other investigators have referred to the hydrolysis

of the glucose-aglycone or β-glucoside linkage rather than to that of C-CN linkage. Selection of the first type of hydrolysis for study may be due to the difficulties encountered in accurately estimating the HCN produced by the reaction. It may be questioned, however, whether it is valid to reason from one to the other type of reaction. In amygdalin, prunasin, and linamarin the glucose molecule is linked to the aglycone through an alcoholic hydroxyl whereas in salicin, helicin, and arbutin, the linkage is through a phenolic hydroxyl. In the first three glucosides there is a nitrile group attached to the alcoholic C atom which is absent in the last three glucosides. These structural differences may cause a difference in the most favorable conditions for enzyme hydrolysis.

It may also be questioned whether the splitting off of the glucose molecule is catalyzed by the same enzyme as is the HCN formation or the nitrile hydrolysis. Prunase, which readily hydrolyzes prunasin, acts very slowly on amygdalin which differs from prunasin only in being a gentiobiose instead of a glucose glucoside and Fischer has shown (22) that amygdalin may be converted into prunasin by the action of yeast maltase which splits off one glucose molecule but does not hydrolyze the nitrile. Rosenthaler (32, 33, 34) concluded that emulsin consists of three enzymes which he termed amygdalase, prunase, and oxynitrilase. The amygdalase but not the oxynitrilase was destroyed by heating emulsin in 5 per cent. solution to 60-65 degrees for ten hours. The filtrate from an emulsin solution saturated with magnesium sulfate contains amygdalase but not oxynitrilase. Bertrand and Compton (10) obtained evidence that the optimum temperatures for the "oxynitrilase" and amygdalase actions of emulsin are different and concluded that two enzymes are present. Armstrong, Armstrong and Horton (4) distinguish between the amygdalase and β-glucosidase activities of emulsin and infer that the production of hydrocyanic acid from amygdalin is a non-enzymic water hydrolysis of the benzaldehyde cyanohydrine produced by the splitting off of the glucose molecules by emulsin. They found that the glucose was produced at a faster rate than the HCN. Auld (7) also found that more glucose was produced in a given time than HCN or benzaldehyde. Krieble (29) studying the asymmetric synthesis of d-mandelonitrile from benzaldehyde and HCN concluded that there may be two oxynitrilases, a dextro, and a levo form. He observed that the glucosidase of wild cherry does not

hydrolize amygdalin or salicin. Should it be confirmed that there are two or more enzymes concerned in the hydrolysis of cyanogenetic glucosides it is quite possible that their optimum pH conditions may be different.

There is also the possibility that acids or bases may affect cyanogenesis not only by altering the pH of the reacting mixtures but also by direct chemical action on the glucosides themselves rendering them insusceptible to attack by the enzyme. Walker and Krieble (38, 39) report that concentrated HCl converts amygdalin into amygdalinic acid; that is, it hydrolyzes the nitrile to R.COOH and NH_3. Dilute hydrochloric and sulfuric acids split off the glucose molecules and leave mandelonitrile. Ten per cent. oxalic acid converts amygdalin into l-mandelic acid plus some of the dl-acid. Alkalies (39) like barium, potassium and lithium hydroxides racemize amygdalin but do not produce d-amygdalin, the change being more complex. Dakin (19) found that cold barium hydroxide converted amygdalin into isoamygdalin which could be hydrolyzed by emulsin, like amygdalin. Smith (35) determined the fact that amygdalin and prunasin are rapidly racemized by methanolic potassium hydroxide and ammonia and less rapidly by aqueous potassium hydroxide. She concludes that the change is due to alteration in the CN group whereby the phenyl group changes from positive to negative. Feist (21) reported that racemized benzaldehyde cyanohydrine is not hydrolyzed by emulsin to HCN and benzaldehyde. Acharya (1) states that what he terms "labile" and "bound" HCN in sorghum are destroyed by 10 per cent. sulfuric acid. Guignard (26) reported that HCl and sulfuric acid hydrolyze phaseolunatin (linamarin) to ammonium formate.

A number of investigators have adopted the technique of adding acids to the macerated plant mixtures before distilling in order to liberate all of the HCN formed. Willaman and West (42) added 5 per cent. tartaric acid. Charlton (16) added 100 cc. of 30 per cent. sulfuric acid to a hot water extract of Burma beans to hydrolyze the glucoside.

Furlong (24) proposed the use of 150 cc. of 10 per cent. sulfuric acid to hydrolyze the alcoholic extract of 100 g. of millet or guinea corn in determining the HCN. Auld (8) used 6 per cent. sulfuric

acid to hydrolyze the alcoholic extract from linseed cake. Brünnich (15) found that the addition of 2 to 3 cc. of diluted sulfuric acid slightly increased the yield of HCN found in sorghums macerated twenty hours with water. Francis and Connell (23) advocated the addition of 50 cc. of concentrated sulfuric acid to a mixture of 50 g. of Sudan grass and 200 cc. of water before distilling the HCN. Alsberg and Black (3) distilled plants with 5 per cent. sulfuric acid in determining HCN. They state ". . . the leaves of *Prunus virginiana* must be distilled with acid four hours before all of the HCN is liberated, whereas in *Andropogon* and *Panicularia* less than one hour is sufficient to liberate all HCN present." Warth (40) heated 300 cc. of water extract of Burma beans with 50 cc. of concentrated sulfuric acid for two hours on the water bath to hydrolyze the glucoside in his method for determining HCN. He found discordant results between this method and hydrolysis by enzyme. Kohn-Abrest (28) in determining HCN in linseed macerated the seed in water with 2 per cent. of HCl for four hours at 37-40 degrees or twenty-four hours at room temperature, distilled the HCN and then added one-tenth of the original volume of HCl and redistilled. His table indicates 10 to 25 per cent. of the total HCN recovered in the second distillation.

The use of strong acids to "liberate" HCN from cyanogenetic mixtures is open to the objection that such procedures are known to cause loss of HCN through conversion of the cyanide into ammonium formate or other products. Bishop (13) found that he could recover not more than 95 to 97 per cent. of the theoretical quantity of HCN from mixtures of KCN and acids. Briese and Couch (14) found that 2 to 30 per cent. of the HCN present was converted into other substances after heating for comparatively short periods with very dilute sulfuric, phosphoric, tartaric, or oxalic acids.

Some acids readily penetrate plant tissues and stimulate enzyme changes. Armstrong and Armstrong (5) found that hydrochloric, phosphoric, oxalic, and tartaric acids do not penetrate the normal leaf from N/2 solutions but that sulfuric acid does. The fatty acids and lactic, benzoic, and salicylic acid readily penetrate the leaf from N/2 solutions. The degree of penetration was measured by the rate of evolution of HCN from cherry laurel leaves. Flax seedlings and currant leaves gave similar results.

Experimental Part

Plants Used

In the studies presented in this paper the plants used were species of sorghum. *Sorghum vulgare* was represented by the varieties hegari and Spur feterita; *Sorghum halepense* by a dried specimen of Johnson grass collected at Woodward, Oklahoma, in 1936. The specimens of hegari and Spur feterita used were grown at the Arlington (Va.) Experiment Station, of the Bureau of Plant Industry. These were collected immediately before use and were not dried. They were minced through a food chopper, mixed, weighed out, and immersed in the acid medium within an hour after collection. For these plants we are indebted to the good offices of Dr. John H. Martin and Mr. R. W. Leukel, of the Bureau of Plant Industry, to whom we express our best thanks. One of these samples was used for each series of determinations and it was necessary to collect another sample for each successive determination owing to the impossibility of making all the determinations at one time on one collection of plant.

Samples of the plant were weighed into pint preservative jars, covered with a definite quantity of the acid solution, at 25 degrees, mixed, and the pH was then taken. The covers of the jars were then clamped on and the jars were placed in an incubator at 37 degrees for twenty-four hours. The jars were then removed, opened one after another, and the pH of the contents taken after cooling to 25 degrees.

The sample was then transferred to a 5-liter flask, 2 per cent. of mercuric chloride in solution was added, the whole was mixed and then diluted to 1500 cc. with boiling water. The flasks containing the diluted samples were connected to the condensers, heated to the boiling point, cooled momentarily, and a slight excess of stannous chloride in solution was added to decompose the mercuric cyanide. Distillation was then started, the volatilized HCN being caught in dilute NaOH. When 400 cc. of distillate had collected the receiver was changed and the first distillate was titrated according to Liebig-Denigès (20) with N/10 or N/50 $AgNO_3$ depending on the amount of HCN present. Distillation was continued as long as significant quantities of HCN were found in the distillate.

The hydrogen ion concentrations of the mixtures were determined by means of the quinhydrone electrode, except for the last two series in which the glass electrode was used.

The errors inherent in the process have been estimated (14) as up to 3 per cent. with green plant and 1 per cent. with dried plant.

Arresting Enzyme Action With Mercuric Chloride

In certain early experiments in which *Prunus serotina* was used the results obtained with different concentrations of acids were irregular and led to the suspicion that the rate of HCN formation during the period intervening between dilution and boiling of the incubated mixture was rapid enough to compensate for differences due to the influence of the acids. The possibility of this occurrence was investigated with the results given in Table 1. Six 25 g. samples of one col-

TABLE 1.—Hydrocyanic acid recovered from incubated samples of fresh *Prunus serotina* leaves diluted with cold and hot water and with mercuric chloride.

Incubated with	Treatment before distillation	HCN calcd. to fresh plant mg%	Dry plant mg%
Water	Diluted with water at 25°	90.6	266
0.1% HCl	Diluted with water at 25°	88.9	261
Water	Diluted with boiling water	84.4	248
0.1% HCl	Diluted with boiling water	82.5	242
Water	Mercuric chloride followed by boiling water	82.1	241
0.1% HCl	Mercuric chloride followed by boiling water	74.6	219

lection of fresh *Prunus serotina* were weighed out, half of them were treated with 140 cc. of water at 37 degrees and the other half with 140 cc. of 0.1 per cent. HCl also at 37 degrees. These were then incubated at 37 degrees for twenty-four hours and then given different treatments on analysis. One of each was diluted to 1200 cc. with water at 25 degrees and distilled. It required twenty minutes for the mixture to reach the boiling point. A second pair was diluted with boiling water, care being taken to avoid loss of HCN, and immediately distilled. The third pair was treated with 0.5 g. of mercuric chloride in solution, diluted to 1200 cc. with boiling water, heated, and when brought to

the boiling point twice the calculated quantity of stannous chloride was added to free the HCN. The purpose of the mercuric chloride was to arrest the action of the plant enzymes instantly. The results showed that considerable liberation of HCN takes place during the process of heating up the diluted sample to the boiling point and that even the addition of boiling water does not instantly stop this reaction. In both series the results were the same; the lower values obtained in the acid experiments are ascribed to repression of hydrolysis by the hydrogen ion concentration.

It was apparent that a serious error would be introduced into the experiments by the irregular formation of HCN during the predistillation period. To remove this error so far as possible all samples were treated with mercuric chloride and boiling water just previous to distillation to stop all enzyme action. The results indicated that this end was accomplished satisfactorily.

Change of pH in an Hegari Mixture With Time

A consideration of the results obtained in the several experiments conducted at different pH levels raised the question which figure could be considered to represent the effective pH of the mixture. The fact that the pH of the mixtures usually changed to an appreciable extent during the twenty-four hours' maceration made it evident that the original pH of the mixture could not be accepted as the representative figure. The same was true of the final figures but for a different reason, namely, that often two or more of the final figures in a single series might be identical or at least not significantly different and yet the corresponding quantities of HCN might be quite different. As examples may be cited the final pH figures for 0.3 and 0.7 g. of sulfuric acid (Table 19) corresponding to 8.7 and 8.4 mg. per cent. HCN, respectively; figures for 0.1 and 0.5 g. of hydrochloric acid in Table 18; figures for 0.1, 0.7, and 1 g. of tartaric acid in Table 14, and for 0.3 and 0.7 g. of sulfuric acid in Table 5. Obviously neither the initial nor the final pH accurately represents the effective pH for the particular mixture under examination.

It was possible that an average of these figures might more nearly approach the true pH. To examine this possibility a typical mixture was made of fresh hegari leaves. This was macerated at 37 degrees and hourly determinations of the pH were made for the first twenty-

six hours. Thereafter determinations were made at longer intervals until 142 hours had elapsed. The data are presented in Table 2. The average figure for the twenty-five determinations during the first twenty-four hours is 5.45 and the average of the initial and twenty-four-hour figure is 5.4, indicating that this average figure represents more nearly than any other the effective pH level of the experiments. From the second to the twenty-first hour the pH remained at 5.5 to 5.4. After the twenty-first hour the pH fell rapidly, finally reaching 4.5 after seventy-four hours at which point it remained constant for 142 hours, when the experiment was discontinued. This constancy following the precipitous fall from the twenty-first to the twenty-sixth hour is of considerable theoretical interest indicating the sudden acceleration of some reaction that was proceeding only very slowly up to the twenty-first hour.

TABLE 2.—pH of a mixture of 100 g. of hegari leaves and 300 cc. of water at 37° at different intervals of time.

Time hours	pH	Time hours	pH	Time hours	pH
0	5.7	11	5.5	21	5.4
1	5.6	12	5.5	22	5.3
2	5.5	13	5.5	23	5.2
3	5.5	14	5.5	24	5.1
4	5.5	15	5.5	25	4.9
5	5.5	16	5.5	26	4.7
6	5.5	17	5.4	74	4.5
7	5.5	18	5.4	92	4.5
8	5.5	19	5.4	96	4.5
9	5.5	20	5.4	142	4.5
10	5.5				

The twenty-four-hour pH is higher in this series than was recorded for other samples of hegari as set forth in Table 9. This is ascribed to the fact that the specimen in question was opened each hour for sampling allowing carbon dioxide to escape and so raising the pH whereas the other samples were kept sealed during the entire incubation period.

(To be continued in March)

IONIZABLE SILVER OR STRONG SILVER PROTEIN IN MILD SILVER PROTEIN

By F. N. Van Deripe and R. A. Konnerth*

WHEN the U. S. P. XI test for ionizable silver or strong silver protein in mild silver protein is applied to the various market brands, the filtrate does not remain clear upon addition of the hydrochloric acid. While the U. S. P. does not specify that it must remain clear and says only that a precipitate shall not form, there is the range intermediate between clear and precipitation which is a source of indefiniteness. Thus, a haze, opalescence, or turbidity may not be a precipitate and therefore may not constitute non-compliance with the U. S. P. XI specification. However, we find that haze or turbidity does result when the hydrochloric acid is added, and interpretation of the test becomes difficult. Consequently, there is a need to revise this test so as to provide for this condition, recognizing that the filtrate will not remain clear and eliminating the troublesome distinction between haze or turbidity without precipitation and actual precipitation.

During the preparation of mild silver protein there is an intermediate stage at which the silver exists entirely in an ionizable form—not entirely as ionized silver but in states of combination such that the silver is ionizable. The silver may exist partly as colloidal silver oxide and partly as silver salts of simple amino acids or as silver derivatives of substances representing intermediate stages of protein hydrolysis. This reaction mixture is subjected to a treatment which converts the silver in these combinations to colloidal silver and then the electrolytes in the solution are removed by dialysis. That should and does serve to remove any small amounts of unconverted, easily ionizable silver as well as other ionizable material. Removal of that ionizable silver existing in a state of combination which yields its silver ions readily proceeds smoothly and completely. However, those combinations which yield silver ions only slowly and to a slight extent do not give up all their ionizable silver within a reasonable practical dialysis time. Therefore, while these solutions, after dialysis, do not contain any easily or appreciably ionizable silver compounds, they do

*Analytical Department of the Chemical and Pharmaceutical Laboratories, E. R. Squibb and Sons, Brooklyn, N. Y.

have in them small proportions of those difficultly and slightly ionizable silver compounds. Products obtained from such solutions by evaporation are not completely free of ionizable silver and will not comply with a limit which permits no ionizable silver; they will contain those small amounts of slightly and difficultly ionizable silver compounds which do not pass out through a dialyzing membrane under practical conditions. Those substances will however respond positively in tests for silver ions because of the fact that these tests are very sensitive and will detect minute amounts of ionic silver. It therefore is necessary, if one is going to take a practical viewpoint, to use a test which while detecting these traces of silver ions will do so under conditions such that the amount of ionizable silver may be estimated, and with the test there must be a limit so chosen that products containing unobjectionable traces will comply and those containing larger, objectionable amounts will not. That has been accomplished in the test described and recommended herein.

This modified test with its limit is, in our opinion and that of one other laboratory where it has been tried, not only adequate but better than any other proposed to date. We are therefore making it available for trial by all interested parties and are recommending it for adoption in a U. S. P. Supplement.

Dissolve 1 gram of the mild silver protein in 10 cc. of distilled water. Add 7 grams of ammonium sulfate and stir occasionally for one-half hour. Filter through quantitative filter paper. Re-filter, if necessary, to obtain a clear and practically colorless filtrate. Obtain as much filtrate as possible, but do not wash the material on the filter. Collect the filtrate in a 50 cc. Nessler tube. Add 25 cc. of a 1-100 solution of acacia.

At the same time make a blank determination as follows: Dissolve 7 grams of ammonium sulfate in 10 cc. of distilled water in a 50 cc. Nessler tube. Add 25 cc. of a 1-100 solution of acacia and then 1.6 cc. of N/100 silver nitrate.*

Then to each of the two solutions in the Nessler tubes add 2 cc. of nitric acid, 2 cc. of dilute hydrochloric acid, and sufficient 1-100 solution of acacia to make both solutions up to 50 cc. Mix thoroughly and let stand for five minutes. The turbidity in the

*The determination may be made roughly quantitative, if several blanks for comparison are prepared containing different amounts of N/100 silver nitrate.

test should be less than that of the blank when viewed crosswise against a black background in indirect light.

It will be noted that this modified U. S. P. XI test provides for a small amount of ionizable silver in mild silver protein and does so in such a way that it can be estimated quantitatively if one wishes. As to the amount of ionizable silver represented by the limit: 1.6 cc. N/100 silver nitrate contains 1.7 mg. of silver which corresponds to 0.17 per cent. in the one-gram sample taken for analysis—granting that this figure is low because the ammonium sulfate precipitate is not washed the true amount would not exceed 0.25 per cent. When it is considered that mild silver protein may contain 19-25 per cent. silver it becomes apparent that with even this latter figure the ionizable silver is only 1.0 to 1.4 per cent. of the total silver.

A limit for ionizable silver in mild silver protein is acceptable only if a product containing the maximum permissible amount is still non-irritating. Such is the case with the limit proposed above. This was determined by application of 10 per cent. solutions to the eye.

A STUDY OF WATERMELON DIURESIS

By Charles Roby, Jules H. Last and Carl Pfeiffer

FROM time to time accounts have appeared in the lay press of favorable results following the use of watermelon juice in relieving the anuria of acute nephritis. In the course of other diuretic studies a series of experiments analyzing the diuretic action of watermelon juice and its extracts were made.

Bliss, Morrison, and Prather (1) performed water balance studies on rabbits in an effort to determine the diuretic response to fresh watermelon juice and concentrates of watermelon juice. Watermelon juice with equal quantities of water as controls were administered to rabbits by stomach tube. The authors report that there was no change in the twenty-four-hour urine output after watermelon juice and on this evidence they conclude that watermelon juice is not an efficient diuretic. They also found that water-bath concentrates of the juice produced intense irritation of the gastro-intestinal and urinary tracts in rabbits.

In 1937, Coon, Noojin, and Pfeiffer (2) reported experiments showing the importance of chloride and water balance in determining the diuretic response of the kidney. They found that 0.4 per cent. to 0.6 concentrations of saline were well tolerated by the gastro-intestinal tracts of dogs and produced the greatest diuresis.

Watermelon juice is composed of approximately 88 per cent. H_2O, 3.6 per cent. glucose, 6.2 per cent. sucrose, and 0.03 per cent. NaCl (3). Rosa (4) has noted a progressive increase in the percentage of solids and total sugars during ripening with a decrease in the percentage of invert sugars.

The following experiments with watermelon juice and its extracts were carried out on dogs which had been operated to produce bladder extrophies and trained to stand quietly in stocks for the duration of the experiments. Urine was drawn at ten-minute intervals from funnels strapped under the fistulæ. The dogs were dehydrated for five hours preceding the experiments and a control period of thirty minutes was allowed before the administration of any fluid. All fluids were at 37 degrees C. and were given by stomach tube in 50 cc/kgm. doses. The animals were used only twice a week to lessen the danger of

kidney damage and allow for the return of salt and water equilibrium. The urine samples from all the dogs were pooled at each ten-minute reading and 5 cc. samples were taken for chloride determination.

Fig. I demonstrates the comparative effects of watermelon juice which had been extracted from fresh watermelons, vacuum distillate of

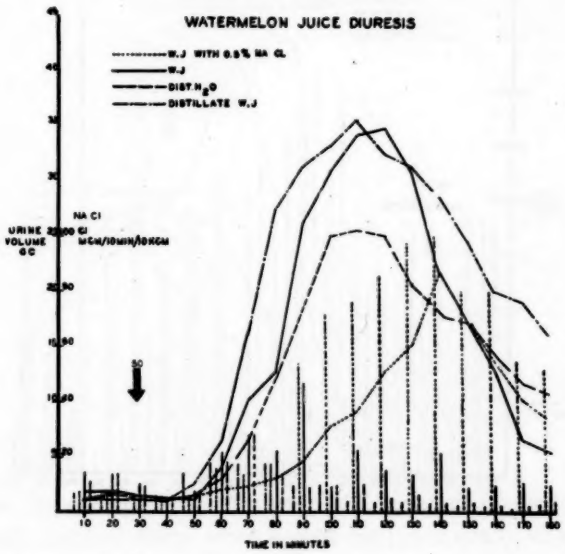

Figure 1

watermelon juice, distilled water and watermelon juice with sufficient NaCl to make the final mixture 0.5 per cent. NaCl. This latter mixture was used to rule out any possible latent diuretic effects of watermelon juice which might be masked by its low NaCl content. The urine chlorides are expressed as mgm./10 min./10 kgm. of dog. It is apparent that both fresh juice and distillate of juice possess some advantage over distilled water as diuretics. The chloride excretion increases and decreases with the diuresis and is the greatest in the case of watermelon juice with 0.5 per cent. NaCl.

Juice extracted from watermelons which had been in the ice box about one month was also used. Fig. II shows the effect of this juice, an artificial juice consisting of 6.2 per cent. sucrose and 3.6 per cent. glucose, distilled water and 0.5 per cent. NaCl. Distilled water and 0.5 per cent. NaCl produced the greatest urine flow, while old juice and artificial juice were inefficient as diuretic agents. In the case of

"old watermelon" juice, at no time did the chloride excretion reach the level attained in the control period while with the artificial juice, the peak of chloride excretion preceded the height of diuresis by thirty minutes.

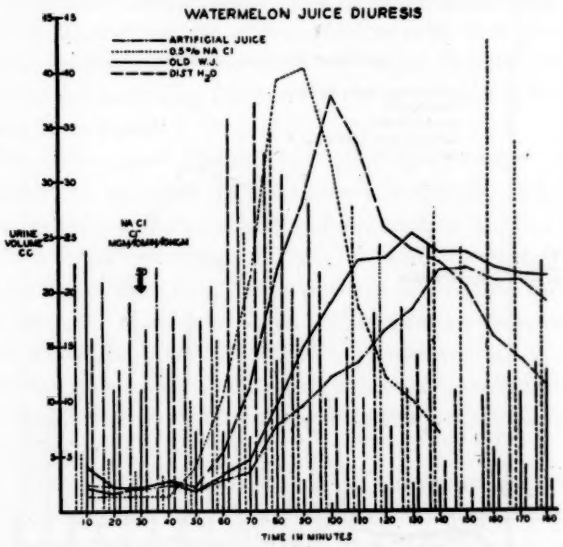

Figure 2

Extracts of watermelon juice and seeds were prepared and tested for their diuretic activity. For this experiment 2850 cc. of fresh juice was vacuum distilled below 50 degrees C. to 250 cc. volume. This was then extracted with 500 cc. 95 per cent. alcohol which precipitated most of the sugars. The sugars were discarded and the alcohol was removed by vacuum distillation and 200 cc. of alcohol was again added to remove more sugar. The residue, after vacuum distillation, was placed in a separatory funnel with 200 cc. of ether. The pigment of the juice dissolved in the ether fraction and the two were separated and concentrated to almost dryness by vacuum distillation. The syrupy residues were then dissolved in propylene glycol and administered as alcohol extract and ether pigment of juice. The seeds were finely ground and extracted with H_2O. They were then extracted with alcohol and ether in the same manner as above. The ether extract of seeds and the ether pigment and alcohol extract of juice were administered intramuscularly in 1 cc. and 2 cc. doses.

The ether pigment of juice produced a slight inhibition in kidney excretion while the ether extract of seeds gave only a normal curve of urine excretion. The alcohol extract of juice exerted an insignificant diuretic action (Fig. III).

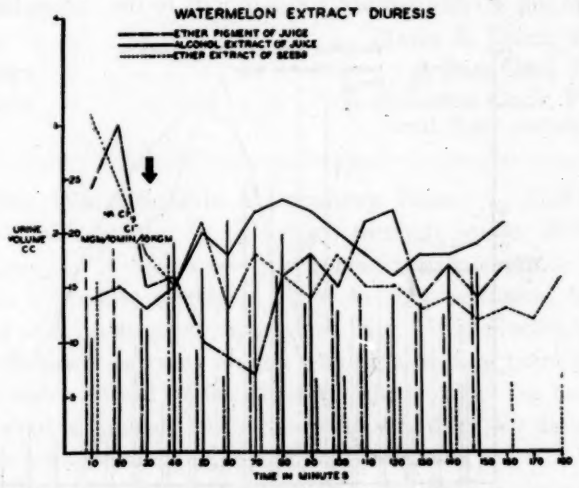

Figure 3

The diuretic response to an alcoholic extract of seeds was compared with distilled water when both were given orally in 50 cc./kgm. doses (Fig. IV). The two curves closely approximate each other indicating that watermelon seeds possess no diuretic potency.

Eleven experiments were performed and, contrary to the findings of Bliss,(1) at no time was there any vomiting or diarrhea indicating gastro-intestinal disorder due to watermelon juice or its extracts. At the end of these experiments, the kidneys of the dogs were tested physiologically by their diuretic response to 200 cc./kgm. of 0.5 per cent. NaCl and except for a hydronephrotic curve in one dog all appeared normal. This hydronephrosis has been confirmed by autopsy and was due to scar tissue contractures around the ureteral orifices. The kidneys themselves, except for the hydronephrosis, appeared grossly normal.

Conclusions

1. Watermelon juice apparently contains a volatile diuretic constituent which is also present in distilled juice but which disappears upon aging of the melon.

2. This volatile component exerts a slight diuretic activity, probably by its irritant action.

3. Extracts of juice and seeds contain no diuretic principle.

4. Vacuum distillates, alcohol and ether extracts of watermelon juice and the whole juice are not injurious to the canine kidney.

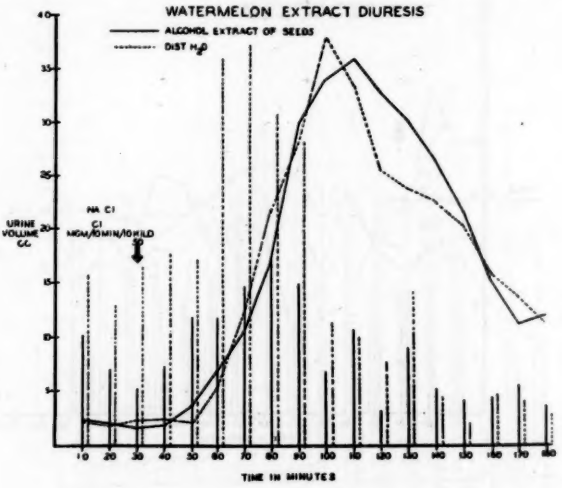

Figure 4

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ABSTRACTS FROM AND REVIEWS OF THE LITERATURE OF THE SCIENCES SUPPORTING PUBLIC HEALTH

Bacteriology . . . . **Louis Gershenfeld, B. Sc., Ph M.**
Biology . . . . . **Marin S. Dunn, Ph. D.**
Chemistry . . . . . **Arthur Osol, Ph. D.**
Pharmacy . . . . . **E. Fullerton Cook, Ph. M.**
and their assistants

A New Water-Soluble Suppository Base. L. Middendorf. *Munch. med. Woschschr. 86,* 95 (1939) through *Squibb Abstr. Bull. 12,* 159 (1939). A high molecular polymerization product of ethylene oxide, a product soluble in water in all proportions, has been established as a satisfactory suppository base. It is practically limitless in medicament-carrying ability. Its high melting point makes it absolutely stable toward summer heat and the tropics. No bad effects were observed in animals treated experimentally for six days with 6 gm. of a 25 per cent. aqueous solution of the base.

Methylene blue incorporated in this new base was excreted in about 70 minutes compared with 150 minutes necessary for excretion when in a cocoanut oil base. Clinically the new base proved more satisfactory as a suppository base than the usual cocoanut oil.

L. F. T.

Drug Therapy in Coronary Disease. Harry Gold. *J. A. M. A. 112,* 1 (1939). The author describes the use and value of drugs in the treatment of symptoms and functional disorders of the heart and circulation. The drugs are as follows:

(1) Nitrites—Nitrites are the drugs of choice in the treatment of the pain of effort angina and offer relief in pain of the acute phase of coronary thrombosis. However, he infers that nitrites are dangerous in the acute phase of coronary thrombosis, because they may further lower the blood pressure. Octylnitrite, newly introduced, has the advantage of being less volatile, less potent, and the period of vasodilation is longer than other volatile nitrites. It may be used in the treatment of effort angina.

(2) Xanthines—The author believes that the xanthines are of questionable value in the relief of cardiac pain, and further disap-

proves the work of other investigators by showing that large doses of aminophylline were of no value. The evidence presented leaves little doubt as to the ineffectiveness of aminophylline, theocalcin, theobromine with sodium salicylate and other xanthines in the treatment of cardiac pain or myocardial infarcation, but they were of value as diuretics in congestive cardiac failure.

(3) Morphine—Morphine is useful in pain due to coronary thrombosis. However, the disadvantage is that coronary thrombosis is complicated by constipation, urinary retention, vomiting, irregular heart beat and stupor. In place of morphine, codeine, dilaudid, pantopon and a mixture of codeine and scopolamine hydrobromide, can be given.

(4) Barbiturates—Barbiturates are useful in coronary disease by reducing nervous excitability. The rapidity of recovery offers no particular advantage. They act by reducing susceptibility of the heart to ectopic rhythms. Large doses cause excitement which defeat the purpose of the sedative.

(5) Digitalis—Digitalis is useful in cardiac failure, auricular fibrillation, possibly paroxysmal tachycardia and in coronary thrombosis. The author states that all coronary patients need not be digitalized. The author also points out that digitalis does not exert any direct constrictor action on the coronary circulation in patients with coronary artery disease.

(6) Diuretics—They are useful for the control of congestive heart failure and attacks of paroxysmal dyspnea.

(7) Quinidine—This drug controls troublesome auricular fibrillation and ventricular tachycardia. It is believed that prophylactic doses of quinidine are without sufficient merit to be used in routine treatment. Intravenous injections are dangerous and should be avoided except in extreme emergencies.

(8) Papaverine, Iodides and Tissue Extracts—Papaverine appears to have little value in the control of cardiac pain. Iodides and tissue extracts are not of much value in the treatment of coronary disease.

Drugs used in emergency treatments are also mentioned.

Quinaldinic Acid as a Reagent for Copper, Zinc and Cadmium. R. J. Shennan. *Analyst 64* (1939). Quinaldinic acid has been proposed as an analytical reagent for the quantitative determi-

nation of a number of metals, and has been recommended as being suitable for the separation of Cu and Cd. An investigation was undertaken to establish the pH range over which complete precipitation could be effected for the metals Cu, Zn, and Cd; and so to define more precisely the conditions for determination.

Determination of Cu: A volumetric solution of $CuSO_4$ was made, and the amount of Cu was determined by the sodium anthranilate method. To a similar sample of $CuSO_4$ was added sodium acetate and glacial acetic acid, the solution was boiled and an excess of an aqueous solution of quinaldinic acid was added slowly, the precipitation was collected forty-five minutes later and weighed. The filtrate was retained for pH determination.

Complete precipitation was obtained over the pH range 2.5 to 6.96. Attempts to extend the range above pH-7 resulted in the precipitation of $Cu(OH)_2$. In the absence of sodium acetate it was found possible to attain pH values below 2, and to extend the range of Cu precipitation to pH 1.5.

Determination of Cd: A sample of $CdSO_4$ was determined by the anthranilic acid method. The procedure for the determination of Cd by the quinaldinic acid method was carried out in the same manner as for Cu.

Complete precipitation of Cd was obtained over the pH range 3.9 to 7.2.

Determination of Zn: A sample of Zn was dissolved in HNO_3 made just alkaline with Na_2CO_3 and just acid again with acetic acid. The Zn was determined by the Funk & Ditt method. The method of precipitation, washing and drying of zinc quinaldinate was similar to that employed for Cu and Cd.

Complete precipitation occurs over the range of pH from 2.3 to 6.5.

The results show that Cu-Zn separations are impossible by adjustment of pH, and that if any separation of Cu from Cd, or of Zn from Cd is possible it should be over the pH range 2.7 to 3.1. When sodium acetate buffer was employed, it exerted a pronounced solubility effect, a parallel case in that of copper anthranilate.

Experiments were made to separate Cu and Zn from Cd. High results were obtained in all experiments owing to the co-precipitation of cadmium quinaldinate. In the separation of Cu from Cd co-precipitation varied from 0.8 to 4.5 per cent, whereas in the separation of Zn from Cd results were inaccurate to the extent of 8 per cent.

From these results it may be concluded that quinaldinic acid offers a rapid, convenient, and highly accurate method of determining Zn, Cd and Cu separately, but it is unsuited for the separation of these metals from each other. A. F. M.

Stearyl Alcohol—Its Advantages as Compared with Cetyl Alcohol. *Chem. Prod. 1,* 111 (1939). Cetyl alcohol has come into widespread use in numerous types of cosmetics and pharmaceutical products. Being a fully saturated compound, pure cetyl alcohol is not liable to rancidity. This is true only of pure cetyl alcohol or of grades which contain as impurities only homologous alcohols.

Stearyl alcohol now available possesses all the good points of cetyl alcohol and exhibits some of them to a greater degree. It also is a fully saturated alcohol and not subject to randicity. Its formula is $C_{18}H_{37}OH$ having a molecule which is longer than cetyl alcohol by two carbon atoms. This seemingly slight difference is definitely important. The greater weight of the molecule is associated with a higher melting point than that of cetyl alcohol and, other things being equal, a less proportion of stearyl alcohol suffices to increase the viscosity of creams and to enhance their stability.

Like cetyl alcohol, stearyl alcohol is a lipoid possessing emollient properties not associated with greasiness. A formula for an emollient cold cream is as follows:

Stearyl Alcohol	20 gm.
Lanolin	50 gm.
White Petrolatum	430 gm.
Olive Oil	40 gm.
Rose Water	460 gm.
Oil of Rose	20 drops

The lipoids are melted and mixed together. The rose water is then run in slowly with constant stirring. When the mixture is cool, the perfume is added and the cream kneaded in vacuo.

Experiments have confirmed the conclusion that stearyl alcohol is superior for the production of creams in which water is absorbed by the lipoid phase. It is clear, therefore, that stearyl alcohol is not merely a substitute for cetyl alcohol but for certain purposes it is definitely better. L. F. T.

A Note on Avocado Pear Oil. A. L. Bacharach and E. Lester Smith. *Analyst 63,* 811-813 (1938). The oil of the avocado pear (*Persea americana*) is now an article of commerce. The flesh of this fruit is a very rich source of oil which may constitute as much as 75 per cent. of the total solids of all the flesh. The oil finds use in the cosmetic industry frequently supported by claims of a surprising nature. These may refer to the high vitamin content of the oil. (*Chemist and Druggist,* March 19, 1938, 128, 347). The article gives a number of cosmetic formulæ involving use of the oil.

The authors were interested in natural sources of fat-soluble vitamins and it seemed to them worth while to examine a sample of avocado pear oil and it was investigated for its content of three fat-soluble vitamins.

Broadly speaking, claims have been made for vitamin D in liberal quantities, richness of vitamin A and statements as to the vitamin E content of the oil are occasionally encountered in commercial publicity matter.

The authors did not look for water-soluble vitamins in the oil, in spite of the occasional appearance of statements that some vegetable oils contain all the vitamins or of similar claims to immunity from natural laws.

Spectrophotometric and use of standard antimony trichloride reagent of the B. P. was used for the determination of vitamin A. The authors found that the amount of biologically active vitamin A and precursors present in the oil itself can be taken as negligible.

Vitamin E was assayed for biologically and the oil found to be completely inactive at the level tested, with the probability that vitamin E was completely absent.

Finally a sample of the oil has been examined for vitamin D by the line test. It was found by this means that the oil itself cannot have contained more than four international units per gram and probably contained less. Although this oil would be quite valueless as a medicinal or commercial source of vitamin D, it is perhaps of some scientific interest that we have found it to contain a little vitamin D. This is presumably to be attributed to solar irradiation of traces of pro-vitamin D.

Emulsification and Chemical Reaction. A. King and L. N. Mukerjee. *J. Soc. Chem. Ind. 57,* T431 (1938). In heterogeneous reactions between two immiscible liquids the velocity may be increased by enlarging the area of interface between the liquids, by stirring, etc. A more efficient method of increasing the interface is to emulsify one liquid in the other. The effect of emulsification of amyl acetate in solutions of alkali on its rate of hydrolysis has been studied using a variety of emulsifying agents. Size-frequency analyses of the emulsions have been made and the area of interface per unit weight of ester calculated in each instance. It was found that the rate of reaction was not quite proportional to the area of interface if different emulsifying agents were used. The specific effects of various emulsifying agents were calculated.

A number of other reactions between immiscible liquids were carried out and in each case the emulsified system was found to react more quickly than the corresponding unemulsified but agitated system.

L. F. T.

The Behavior of the Yellow Fever Virus in the New Jersey Mosquito. B. L. Bennett, F. C. Baker and A. W. Sellards. *Science, 88,* 410 (1938). Considerable experimentation has been done by the authors on the New Jersey mosquito, *Aëdes triseriatus,* as an outgrowth of the question raised by Dr. Smith of New Jersey in 1904 that this mosquito may serve as a vector of yellow fever. This mosquito is found from Maine to Florida and westward to Montana, an area which lies outside the endemic zone of yellow fever.

Baker succeeded in establishing a colony of these mosquitoes at Cornell University. The first experiment was conducted at the Harvard Medical School in the autumn of 1935. About thirty-five mosquitoes were given an infected feeding on a monkey dying of yellow fever. After an incubation period at about 28 degrees C., seven of these mosquitoes were living and six fed on a healthy monkey. Six days later there was an indefinite febrile reaction (104.1 degrees F.) on one day only, but the animal remained in excellent condition for about a month. On the thirty-sixth day, however, the monkey died of yellow fever.

Meanwhile, the colony at Cornell had been discontinued and it was not feasible to resume the work until March, 1938, when another colony was reared from larvæ collected near Ithaca, N. Y. Mosquitoes which had previously taken an infective blood meal were allowed to feed on four monkeys. These animals showed no febrile reactions, but two of them died of yellow fever after intervals of ten and thirteen days. Blood taken from the two surviving monkeys failed to protect mice against yellow fever. The two monkeys which survived were bitten by mosquitoes which were kept for fourteen to fifteen days at about 28 degrees C., whereas the two monkeys which died were infected by mosquitoes which were incubated at 37 degrees C.

Ten mosquitoes which had ingested infective blood of dying monkeys were tested for virus after incubation periods of thirteen to sixteen days. Each mosquito was ground in a mortar with a little serum-saline, and injections were made intracerebrally in white mice. The virus was recovered from six of these ten mosquitoes.

Briefly, the virus of yellow fever in its ordinary form was transmitted to monkeys (*Macacus rhesus*) by *Aëdes triseriatus*, and there was some evidence of attenuation of the virus in this mosquito.

In nature, as far as we know, this mosquito has never transmitted yellow fever, but if yellow fever should gain a foothold on our Eastern shore the possibility that this widespread species might transmit the disease is worthy of our attention.

The Treatment of Pneumococcic Pneumonia with Sulfapyridine. H. F. Flippin, J. S. Lockwood, D. S. Pepper and L. Schwartz, *J. A. M. A. 112*, 529 (1939). The encouraging results of sulfanilamide therapy in infections due to hemolytic streptococcus, gonococcus, meningococcus, B. coli and the slight effect against the pneumococcus has led to the hope that a similar compound would become available which would become available which would be effective in the treatment of pneumococcic diseases.

The fact that the bacteriologic similarity of the pneumococcus is so close to the hemolytic streptococcus and that a similar immunologic process of host resistance in the two types of diseases exists further strengthened the hope that such a drug would be found.

With this hope in mind, Ewins and Phillips were eventually able to synthesize a compound with the desired effects—Sulfapyridine. The experimental and clinical use has already been the subject of a number of highly encouraging reports in the English medical literature.

It is still under clinical observation in this country and the available reports have shown quite satisfactory results.

It has been reported that sulfapyridine was chemotherapeutically active in experimental infections in mice against pneumococci of types I, II, III, V, VII and VIII and was also as effective against hemolytic streptococci and meningococci as sulfanilamide. Evidence has also been published that sulfapyridine in vitro (in concentrations which could be obtained therapeutically) would greatly increase the killing power of normal human blood against pneumococci and streptococci. The low toxicity of the drug for animals is particularly noteworthy.

The absorption of the drug from the gastrointestinal tract is more rapid than is that of sulfanilimide, but it is excreted more slowly. Sulfapyridine is only sparingly soluble in water (0.1 per cent.), but its presence in the blood may be detected as soon as thirty minutes after ingestion. The relatively low toxicity might therefore be explained on the basis of limited and slow absorption. The toxic effects which have been noticed were generally mild and consisted of cyanosis associated with methemoglobinemia, nausea and vomiting.

The clinical reports from one hospital in England show quite satisfactory results. Out of 200 patients, 100 were taken as control patients and received the regular treatment while the other 100 were given treatment with sulfapyridine. The control group showed a mortality rate of 27 per cent. while the group treated with sulfapyridine showed a mortality rate of 8 per cent. and six of the latter failed to receive an amount of the drug which was considered to be adequate. In the majority of the cases an initial dose of 2 gms. was followed by 1 gm. every four hours until a total of 25 gms. had been administered. The record of any patient which died within twelve hours after diagnosis was excluded from the records.

The reports from several Philadelphia hospitals show that sulfapyridine therapy has been carried out in 100 cases of typed pneumococcic pneumonia with only four deaths in the series, three of which

were in type III infections. There were eight cases of bacteremia with one death. A conspicuous effect of the drug seemed to be its ability to bring about, within twenty-four to forty-eight hours, a critical drop in temperature followed by prompt clinical improvement.

In pneumonias from which pneumococci may be typed, the drug has seemed to be quite uniformly effective, though perhaps less effective in type III than in all other types encountered. If sulfapyridine is used with regard for its toxic possibilities, and if the patients in whom it is used are thoroughly studied and carefully followed, it is a therapeutic agent with a satisfactory margin of safety.

B. K.

Warning of Ether Explosions. Von Tandberg. *Chem. Ztg. 62,* 731 (1938) through *Pharmaz. Zentrh. 80,* 9 (1939). Certain peroxides formed in ether, notably dehydroxy-ethyl-peroxide ($CH_3.CHOH.O_2.CHOH.CH_3$) and polymers of ethylideneperoxide $(CH_3CHO_2)x$, give rise to dangerous explosions without ignition during heating. These products are formed if the ether, especially a sample containing aldehydes, is allowed to stand in the sunlight or in contact with air over a period of time. Because of the presence of such peroxides, ether should be tested for purity before each distilling. The presence of peroxide colors ether blue when it is shaken with a sulfuric acid-dichromate solution; or liberates free iodine from acidified KI solution; or gives a yellow color with titanic sulfate. To remove the peroxides for use, the ether is shaken with a solution of acidified ferrous sulfate to form the aldehydes, which are removed with chromic acid followed by alkali. The purified product is stored in the dark over soda lime. The presence of small amounts of hydroquinone or pyrogallol (1:5000) retards the peroxide formation.

W. K.

BOOK REVIEWS

Done by persons, unafraid to upbraid, but perfectly willing to give praise where praise is really due.

The Extra Pharmacopœia (Martindale), 21st edition, Vol. II, Pp. xxxvi + 1148. The Pharmaceutical Press, 23 Bloomsbury Square W. C. 1, London.

Volume I of this edition appeared about two years ago and it will be recalled that Volume I is concerned almost entirely in describing the composition and therapeutic applications of drugs, chemicals and biological products. Volume II from the standpoint of the pharmacist and chemist covers a field of even greater significance.

The Extra Pharmacopœia deals with analytical procedures and official standards of not only the B. P. and B. P. C. but also the U. S. P. XI and the French Codex. To the analyst who is seeking for an alternative method of assay no better reference could be cited.

Formulas of many proprietaries are given, both those disclosed by the manufacturer as well as others representing an analysis of the product. This information is unique and found in but few available references.

The nomenclature of organic compounds is considered, organic qualitative analysis, hydrogen-ion concentration, fluorescence analysis, chromatographic analysis, methods used in clinical chemistry, an excellent discussion of food and nutrition including vitamins, bacteriological notes and technic, X-ray diagnosis and therapy and other such varied subjects.

The reviewer is quite impressed with the numerous fields so admirably treated in this volume and it is doubted whether any similar reference is available to pharmacy. L. F. TICE.